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THE CHANGE IN THE ACTIVITY OF THE ENDOCRINE GLANDS IN EXPERIMENTAL RADIATION PATHOLOGY

[Following is a translation of an article by Corresponding Member of the AMS USSR Professor P. D. Gorizontov and T. N. Protasova in Arkhiv Patologii (Archives of Pathology), Vol. 22, No. 4, 1960, pages 3-14.]

As a result of the action of ionizing radiation on the organism, varied functional disturbances arise which affect all the systems and organs, among which a large place belongs to the glands of internal secretion, regulating the most diverse processes of life activity.

The morphological changes, arising in the endocrine glands after irradiation, have been described in the monograph of N. A. Krayevskiy (1957). There are no works in the Soviet literature dealing with the generalizing characterization of the incretory disturbances setting in in various glands after irradiation; this is possibly explained by the fact that there is still insufficient clarity in these questions.

Adrenal Hormones

Fluctuations in the content of cholesterol and ascorbic acid in the adrenals indirectly indicate a change in the secretions of the adrenal cortex after irradiation. A diminution in the quantity of these ingredients in the adrenals is taken as an indirect index of intensification of the incretory activity of the adrenal cortex. Investigations which have been carried out have shown that the quantity of cholesterol in the tissue of the adrenals of rats after systemic irradiation with X-ray rays in lethal doses is already diminished one hour after irradiation, remaining at a low level up to two to three days; it then is raised and again falls in the terminal period (Pratt and others, 1947; K. A. Tret'yakova, 1957; B. A. Fedorov, L. F. Semenov, 1957). Analogous changes were also found in the content of ascorbic acid (Wexler and others, 1952; L. Ya. Zhorno, 1956; L. V. Bozhenko, 1957). The diminution in the quantity of ascorbic

acid was particularly pronounced in the presence of sagittal half-body irradiation in rats in a dose of 625 r; it should be noted that in these cases the diminution in ascorbic acid was quantitatively identical on both sides -- the irradiated and the nonirradiated (Wexler and others, 1955). According to the data of some authors (Hochman and Block-Frankenthal, 1953), the changes in the content of ascorbic acid in the adrenals of rats do not quantitatively depend on the irradiation dose: in the presence of irradiation in a dose of 50 r the lowering amounted to 20.2 percent, while in the presence of a dose of 1,000 r -- altogether to 26.7 percent. Other authors (Desjardins, 1928; Birkner and others, 1954) consider that the diminution in the quantity of ascorbic acid in the tissue of the adrenals proceeds only after irradiation in doses, for exceeding therapeutic doses, and that the magnitude of the diminution depends on the magnitude of the irradiation dose.

The diminution in cholesterol and ascorbic acid in the adrenals of rats also proceeded after irradiation of the region of the hypophysis or the midbrain in a dose of 200 r, but was pronounced only in the course of the first three hours after irradiation (Baldini, 1958).

An indirect indication of a change in the secretion of corticosteroids after irradiation is the increase in the synthesis of cholesterol in the cortical substance of the adrenals of rats one day or more after irradiation (Hanel and others, 1957; K. A. Tret'yakova and D. E. Grodzenskiy, 1959). G. S. Lykova (1947) by the autoradiographic method and with the use of S^{35} detected an increase in the protein metabolism in the cells of the cortical substance of the adrenals at one, five, and ten days after the irradiation of rats with gamma rays in a dose of 700 r, a fact which also may be associated with a change in the secretory activity. The data presented to a certain extent correspond with the results of the experiments of A. B. Tinkikh (1959), who, in accord with the method proposed by Ingle, studied the functional state of the adrenal cortex of irradiated guinea pigs on the basis of the change of the work capacity of the skeletal muscles. The investigations of A. V. Tinkikh have shown biphasic changes: in the first two to three days after irradiation -- a rise, and beginning with the seventh day -- an acute lowering of the activity of the adrenal cortex.

However, it should be noted that the work capacity of the muscles is only a conventional index for determining the functional activity of the adrenal cortex. According to the data of Portel and others (1959), disturbances of the work capacity of mice, arising after irradiation, depend on changes in the hormonal activity of the hypophysis and the

thyroid gland.

In the presence of irradiation of isolated adrenals of calves in vitro with the gamma rays of Co^{60} in doses of the order of 2,000-3,000 r, a considerable lowering of the secretion of corticosterone, hydrocortisone, and other steroids was noted, although at the same time no appreciable morphological changes were detected in the cortex. The stimulation of the irradiated adrenals via the introduction of ACTH did not evoke the increase in the secretion of corticosteroids which is characteristic of the intact gland; there are grounds for assuming that the lowering of the secretion of hormones is associated with a disturbance of the specific enzymatic activity of the biosynthesis of corticosteroids -- of the capacity to introduce OH-groups at the 11β-, 17a-, and 21 carbon atoms, and also to oxidize the Δ^5-3β-OH groups to a Δ^4-3-3keto group (Ungar and others, 1955; Rosenfeld and others, 1955). However, in the presence of the investigation of the adrenals of calves irradiated with gamma rays of Co^{60} in vivo (dose 600 r), other results have been obtained (Rosenfeld, 1958). In the adrenals of calves, which were excised before the slaughter of the animals, the quantity of 17-oxycorticosteroids not only was not lowered (in the presence of the perfusion of the adrenals both with the addition of ACTH, and also without it), but even was somewhat raised.

On the basis of the data presented one can assume that, in the first place, the secretion of corticosteroids is changed variously in the presence of the irradiation of the adrenals in vitro and in vivo and that, in the second place, in the presence of irradiation in vivo the secretion of the adrenal cortex is changed depending on the magnitude of the irradiation dose, the severity of the disease, and the initial state of the organism; apparently the secretion is different for each given moment of irradiation injury. Certain investigators have tried to obtain more exact notions concerning the change of the hormonal activity of the adrenal cortex via a quantitative determination of the hormones in the urine and in the blood. However, the study of the qualitative changes of the secretion of the corticosteroids can have special significance.

In the presence of the study of the excretion of corticosteroids and 17-ketosteroids with the urine no answer was obtained to the questions posed above, since different authors obtained different experimental results. In the presence of the irradiation of white mice with X-rays in doses of 100-800 r an increase in the excretion of cortico- and ketosteroids with the urine was noted in proportion to the increase in the irradiation dose; above 1,000-1,200 r a lowering of the excretion of corticosteroids even occurred

(Wilhelm, 1955; Rajewsky, 1956). In rabbits the excretion of 17-ketosteroids after systemic irradiation in a dose of 1,500 r fell in the course of the first five days after irradiation (Maurer and Mense, 1955) and particularly before death (B. P. Golovin and O. K. Dokusova, 1957). In dogs, according to some data, the excretion of 17-ketosteroids was increased in the period of five to 12 days after irradiation with X-rays in a dose of 300 r (Lawrence, 1949), according to others -- it was not changed after systemic irradiation in a dose of 350 r (Duffy, 1952). In castrated male guinea pigs after their irradiation with X-rays in doses of 750 and 100 r the excretion of C_{21}-steroids (corticosteroids) with the urea was considerably increased on the first to second day after irradiation, and then was lowered to normal or even below normal (Brayer and others, 1954).

The change in the excretion of 17-ketosteroids and 11-oxycorticosteroids with the urine was also noted in human beings, subjected to X-ray therapy for malignant neoplasms (Pohl, 1953; Bellion and Cravetto, 1956).

Somewhat more unambiguous data have been obtained in the investigation of the content of corticosteroids in the blood after irradiation. In individuals after X-ray therapy for cancer (Notter and Gemzell, 1956) the quantity of 17-oxysteroids in the blood was considerably increased. In the blood of apes, irradiated with X-rays in doses of 400 and 800 r (French and others, 1954, 1955), as well as in the blood of orradiated rabbits (B. M. Varshavskiy and others, 1956) and dogs (Bowers and others, 1952) the quantity of hormones was also considerably increased. This increase was not regular throughout the course of the entire period of radiation sickness, but was of a cyclical character.

Interesting data were obtained in the investigation of the content of steroid hormones in the blood, flowing out from the adrenals of irradiated animals. In the adrenal blood of rabbits, irradiated with X-rays in a dose of 1,100 r, already at three hours after irradiation the total quantity of corticosteroids is increased by one and one-half times (L. V. Orlova and V. M. Rodionov, 1957). The increase in the concentration of corticosteroids proceeded not at the expense of corticosterone -- the basic cortical hormone of rabbits, but at the expense of another, still not identified steroid (compound X). The content of compound X and of hydrocortisone remained raised throughout the entire duration of the radiation injury (Fig. 1). It is possible that it is not the change in the absolute quantity of hormones secreted after irradiation but the disturbance of the usual ratio of the individual hormones that has fundamental significance.

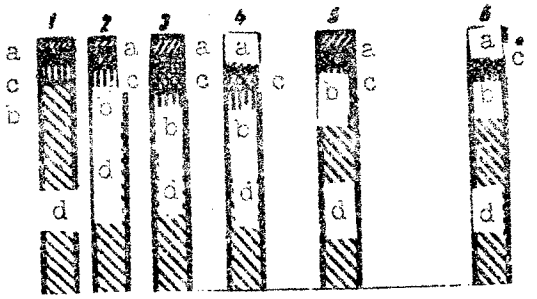

Fig. 1. Ratio of the concentration of corticosteroids in the adrenal blood of rabbits at various periods after irradiation.

1 - normal, 2 -- after 3 hours, 3 - after 24 hours, 4 - after 46 hours, 5 - after 3 days, 6 - after 10 days.

a - corticosterone; b - compound X; c - "Aldosterone"; d - hydroxy corticosterone.

It is well known that various types of hormones of the adrenal cortex regulate different links in metabolism, and that a deficit or a hypersecretion of one or another hormone can influence a corresponding lowering or raising of metabolism.

In the adrenal blood of rats, irradiated with X-rays in a dose of 650 r, in the first hours after irradiation the quantity of corticosterone was considerably lowered, entirely disappeared toward the third hour, and then gradually increased, reaching normal toward the second day (M. A. Larina and T. S. Sakhatskaya, 1957, 1958). It turned out unexpectedly that in dogs, irradiated with X-rays in doses of 650-700 r, changes of the total quantity and in the ratio of the concentrations of different fractions of hormones were absent in the adrenal blood (L. V. Orlova and V. M. Rodionov, 1957).

In the study of the changes in the secretory activity of the medullary part of the adrenals, great methodological difficulties are encountered. A phasic change in the content of adrenal in the blood and aqueous humor of the eye has been shown by the investigations of A. F. Maslova on irradiated rabbits (1958). Initially there occurred an acute increase in the content of adrenalin, then its fall, temporary normaliza-

tion, and shortly before death of the animal another rise with a particularly sharp rise on the day of death, A. V. Tonkikh (1959), in investigating the vascular reaction to pain stimulation in irradiated rats, came to the conclusion that the function of the medullary layer of the adrenals is lowered after systemic irradiation in a dose of 800 r.

Secretory Activity of the Hypophysis

Although all investigators attach great significance to change of the secretion of the hypophysis in the development of radiation injury, the character of change of this secretion has, however, still been insufficiently studied. It is well known that in the presence of systemic irradiation of rats and guinea pigs degenerative processes develop in the hypophysis, which embrace chiefly the beta cells of the anterior lobe (Korson and Botkin, 1954; Ye. A. Moiseyev, 1957). In human beings in the presence of local irradiation of the hypophysis with the object of completely terminating its function, very large irradiation does are necessary (Tobias and others, 1954; McCombs, 1957).

In the presence of the irradiation of a suspension, prepared from dried hypophyses of frogs, there initially occurred a rise in the gonatodropic activity, and then, as the dose was increased, a depression of this activity (L. A. Kashchenko, 1956). In the presence of irradiation of the region of the hypophysis in rats in doses of 100 and 200 r, the gonadotropic activity was insignificantly changed (Freed and others, 1948); systemic irradiation of rabbits with gamma rays in doses of 750 and 1,100 r led to a lowering of the gonadotropic activity, which depended on the magnitude of the irradiation dose (Lane and others, 1954). The gonadotropic function of the hypophysis of frogs did not change after systemic irradiation of the frogs with gamma rays in doses of 7,000-10,000 r (E.Ya. Grayevskiy and A. A. Neyfakh, 1956).

The content of ACTH in the hypophysis of rats did not change appreciably after systemic irradiation in lethal doses (M. A. Larina, E. R. Bagramyan, 1959). Systemic irradiation of rats with X-rays in doses of 500 and 800 r did not change the secretion of the thyrotropic hormone of the hypophysis. However, the hormonal action of the hypophysis on the thyroid gland is retarded, evidently, thanks to the hypersecretion of cortisone which arises after irradiation (Betz, 1954). In experiments on irradiated guinea pigs A. V. Tonkikh detected, that suppression of the function of the adrenals after irradiation does not depend on insufficiency of ACTH, since the administration of the latter did

not avert the depression of the functional activity of the adrenals.

Sex Glands

A large number of works have been devoted to the elucidation of the influence of irradiation on the sex glands. An appreciable lowering of the excretion of sex hormones with the urine after X-ray irradiation of the ovaries and the hypophysis has been shown in cancer patients (R. M. Izabolinskaya and Ye. Ye. Chebotarev, 1953; Piazzi, 1956). After the systemic irradiation of rabbits, guinea pigs, rats, and mice in lethal doses, pronounced degenerative changes were detected in their tests, and the character of the degeneration did not depend either on the magnitude or on the power of the dose (L. V. Funshteyn, 1956; Spalding and others, 1957). The systemic irradiation of apes led to considerable changes of the nuclear apparatus of the cells of the tests, and these changes remained for a long time after irradiation (G. G. Tinyakov and M. A. Arsen'yeva, 1958; G. G. Tinyakov, M. A. Arsen'yeva and Yu. S. Bocharov, 1958). In the presence of systemic irradiation of cats in doses of 600 - 1,800 r destructive changes of the nerve fibers and terminal neural apparatus in the testes were observed (A. M. Rastvorova, 1958). Chronic irradiation of mice evoked the same attack on the spermatogenic /semerodniy/ epithelium, as did acute irradiation; however, under these conditions, recovery proceeded more slowly (G. M. Ronichevskaya, 1959). Systemic irradiation of frogs changed the reaction of the testes to the gonadotropic hormone of the hypophysis (L. A. Kashchenko and A. D. Pushnitsyna, 1953). In the presence of local irradiation of the testes in rats and mice there proceeded the same changes in the sex glands, as well as in the presence of systemic irradiation (Fogg and Cowing, 1952; A. M. Alekseyeva and N. M. Timofeyeva, 1959). Screening of the testes in the presence of systemic irradiation of rats furnished protection against disturbance of spermatogenesis (B. A. Fedorov, 1959).

The results of an investigation of the fertility of males after irradiation correspond to these data. The irradiation of male rabbits in comparatively low doses (100, 200, and 300 r) acts negatively on the reproduction of progeny: in the presence of mating the irradiated males with unirradiated females the mortality of the embryos amounted to 32.7 percent, while in the control -- to zero percent (Murphree and others, 1952). A lowering of the fertility was also noted after irradiation of male mice in doses of 400 and 200 r (N. I. Nuzhdin and others, 1955). The steril-

ity, which arose in the presence of X-ray irradiation of mice, is of a hereditary character (N. I. Nuzhdin and others, 1955).

The functions of the female sex glands are also disturbed after irradiation. Systemic X-ray irradiation of female mice considerably lowered the frequency of estrus in them and diminished the number of cycles; the change of the activity of the sex glands set in beginning with a dose of 50 r and the degree of disturbance was directly proportional to the irradiation dose (N. I. Nuzhdin and others, 1955; N. I. Shapiro and others, 1956). In the presence of a comparison of the effects of systemic irradiation, irradiation of the head and region of the ovaries, it was established that injury of the ovaries occurs basically because of the direct influence of the irradiation (O. N. Petrova, 1958). At the same time, ovaries in a state of functional activity are more sensitive to irradiation than in a state of rest (L. A. Kashchenko and A. D. Pushnitsyna, 1956). Complete sterilization is reached in the presence of doses of the order of 2,500 - 3,000 r for female rabbits and 2,200 - 4,400 r for female rats (Desiave, 1954; Mandl and Zuckerman, 1956).

Fractionated doses, according to some data (O. N. Kitayeva, 1958), somewhat lower the injurious action of irradiation, but according to other data (Desaive, 1954) -- increase it. It is evident that this effect depends on the magnitude of the fractionated doses, since large doses evoke irreversible changes, while the use of small doses proceeds on a background of constant repair. In the presence of fractionated irradiation the female rats proved to be more radiosensitive in relation to fertility than males: the fertility of males in the presence of irradiation in a dose of 10 r per week was not changed, while in females -- it was considerably lowered, and after 48 weeks there set in complete sterility (Rugh, 1954). This effect can be associated with the circumstance that the cause of sterility in females is only injury of the ovary cells, while for sterility of the males many different factors are necessary (H. Langendorff, and M. Langendorff, 1957).

Thyroid Gland

The irradiation of animals also influences the function of the thyroid gland. According to morphological data, after the systemic irradiation of rats and mice in lethal doses during the first day there occurs a certain stimulation of the thyroid gland, which is replaced by a depression which is the more profound, the greater the irradiation dose (L. A. Kashchenko, 1956). The profound degenerative changes, right up to necrosis, indicated depression (Betz, 1952;

Botkin and others, 1953; Ye. A. Lyalin, 1956). The basic metabolism, which was raised in the early periods after irradiation and fell before death, was changed in a parallel fashion (V. A. Kiselenko, Ye. I. Makovskaya, 1959). The administration of thyroxin to rats before irradiation considerably accelerated and increased their death after X-ray irradiation in a dose of 700 r (Krahe, Kunkel, 1958).

The inclusion of radioiodine (I^{131}) in the thyroid gland has been used by many investigators for evaluating the changes which set in after irradiation. After the systemic X-ray irradiation of rats in a dose of 800 r, a lowering of the fixation of I^{131} by the thyroid gland was noted which was most pronounced one day after irradiation, a circumstance which could indicate a change of the secretion of thyroxin; however, the character of this change is still not clear (Closon, Betz, 1954; Ye. A. Kolli, 1959). The lowering of the inclusion of radioiodine in the thyroid gland also took place when the region of the neck and hand was screened in them in the presence of systemic irradiation (Barth, Wolf, 1956). In the presence of the irradiation of only the region of the thyroid gland in rats, the absorption of I^{131}, on the contrary, was raised, and in the region of doses of 3,000 - 6,000 r the intensity of the increase in the inclusion of radioiodine was proportional to the irradiation dose and the time which had passed from the moment of irradiation (Hursh and others, 1951; Landau and others, 1953).

In the presence of the investigation of the consumption of oxygen, and also of the histochemical determination of the activity of succinic dehydrase and the content of nucleic acids in the thyroid gland of rabbits after irradiation of the glands in a dose of 1,500 r, it was established that a certain inhibiting function of the glands after irradiation can be a consequence of injury of the mitochondria systems (D'Alessandro and Fusi, 1956). The administration of radioactive iodine in proportion to the increase of its quantity also made a difference in the state of the thyroid gland: a dose of I^{131} of 1 uc after 48 hours considerably shifted the isoelectric point of the thyroid cells of rats toward the acidic side, and the sorbtion capacity of the cells simultaneous grew considerably -- after 12 hours it exceeded the normal twofold (Yu. V. Krivobok, 1956).

On the question of the influence of irradiation on other glands of internal secretion, the literature data are few and fragmentary. The irradiation of an isolated pancreas in vitro and the local irradiation of the region of the pancreas led to wave-like fluctuations in the secretion of enzymes (A. Ya. Bogayevskiy and B. Gol'dshteyn, 1928; Danegger, Poschl, 1955); there are still no definite data concerning

change in the secretion of insulin. In the presence of local irradiation of the parathyroid glands in rabbits (A. A. Tseytlin, B. N. Mogil'nitskiy, 1935) no changes in the content of calcium in the blood were successfully determined; according to the data of other authors (A. Ya. Bogayevskiy, Ye D. Manucharova, 1929), the content of Ca is changed in a wave-like manner.

The Influence of the Endocrine System on Certain Processes in the Presence of Radiation Sickness

As is evident from the data presented, the influence of ionizing radiations on the animal organism lead to extraordinarily complex changes in the hormonal secretion of the glands of internal secretion. The influence of the changed secretion on various functions and processes of metabolism is still more complex in the irradiated organism. This question is illuminated incompletely and often in a contradictory manner in the literature.

A majority of the authors assign a basic role in the change of the reaction of the irradiated organism to the hypophysis - adrenal cortex system and particularly to the steroid hormones of the adrenal cortex. Actually, the role of these hormones in the organism is very important, while their action is remarkably diverse. There is no doubt that the corticosteroids participate in the disturbances of the salt-water metabolism, which sets in after irradiation. In rats irradiated with X-rays in a dose of 400 r, adrenalectomy retarded the development of polyuria (Pentz, 1957). The reaction of rats, irradiated in a dose of 700 r, to water loading revealed undular changes of diuresis, depending, probably, on disturbances of secretion of the mineralocorticoids (Ye. B. Pavlova and A. Ye. Rabkina, 1957). The change in the normal Na/K ratio in the urine of irradiated rats also attests to this (T. I. Ivanenko, D. E. Grodzenskiy, 1959). It is well known that in totally irradiated animals the excretion of nitrogen with the urine is considerably increased. The increase in the nitrogen in the urine also sets in after local irradiation of the regions of the adrenals in rats, even in the presence of a dose of 50 - 75 r (Lafarque and others, 1953; Thoyer-Rozat and others, 1954). In the presence of the irradiation with a dose of 800 r of adrenalectomized rats, the azoturia on the fifth to seventh day after irradiation which is characteristic of intact animals did not set in (Betz and Jehotte, 1954). The data presented indicate the participation of corticosteroids in the intensification of the breakdown of proteins after irradiation. However, this participation can be associated only with some

sort of definite links of the nitrogen metabolism, since the increased excretion of allantoin and uric acid in the irradiated rats does not depend on change of the secretion of corticosteroids (Jackson and S. Entenman, 1958).

It is still difficult to state the role of the corticosteroids in the characteristic change in the fractional composition of the proteins of the serum, evoked by irradiation. There is no doubt that the steroids of the adrenal cortex influence the synthesis of gamma-globulins and, probably, on the elaboration of antibodies. This is shown in experiments on mice, irradiated with X-rays in a dose of 300 r and which had received cortisone (Werder and others, 1957). The administration to healthy mice of adrenal cortex extract or their irradiation with X-rays in a dose of 200 r led to a rise in the total quantity of proteins of the serum after three to six hours without change in their fractional composition (Milne, White, 1949). ACTH clearly raised the content of SH-groups in the proteins of the liver, lowered after irradiation of rats with a dose of 650 r (Ye. M. Kedrova, 1956).

One should particularly dwell on the question of the influence of the hormones of the hypophysis and the corticosteroids on hematopoiesis in the irradiated animals. The removal of the hypophysis in rats three weeks before irradiation with X-rays in a dose of 500 r led to a greater lowering in the number of erythrocytes and reticulocytes, and in the hematocrit reading and the hemoglobin percent after irradiation than in intact animals. The quantity of leucocytes fell identically in the hypophysectomized and the intact rats (Baker and others, 1955). However, hypophysectomy by itself, evokes an increase in the quantity of leucocytes in the peripheral blood by a factor of approximately two, and consequently in determining the degree of the fall in the quantity of leucocytes in comparison with the initial figures before irradiation, it is impossible to speak of an identical leucopenia. Thus, according to our data, in the hypophysectomized rats on the third day after systemic irradiation in a dose of 100 r the quantity of leucocytes fell to 38 percent, while in intact rats, irradiated with that same dose, it only fell to 77 percent of the initial magnitudes before irradiation (Fig. 2). The hematological changes are accompanied in the hypophysectomized animals by an increase in the severity of other clinical signs of radiation disease (hemorrhage, diarrhea) and by the perishing of individual irradiated animals, which was not observed in the intact animals, irradiated in a dose of 100 r (P. D. Gorizontov, A. A. Grafov, 1960). Consequently, the removal of the hypophysis sharply raises the radiosensitivity of the animals.

It should be noted that after systemic irradiation in a dose of 100 r the lymphopenia was more pronounced in absolute and in relative figures (see F. 2) in the hypophysectomized rats in comparison with the intact irradiated rats. This indicates that the reaction of the lymphoidal tissue arises in the irradiated animals without hormonal influences of the hypophysis (P. D. Gorizontov, A. A. Grafov, 1960). The intensification of the hormonal activity of the adrenal cortex, arising under the influence of ionizing radiation, as well as in the presence of the action of other pathogenic stimulants, exerts an undoubted influence on the formation of the reaction of the lymphoidal tissue. However, a distinctive trait of radiation influence is the fact that the influence of the adrenals on the reaction of the lymphoidal tissue has a limited significance, particularly in the presence of lethal doses of irradiation.

The irradiation of rats and mice with lethal doses evokes acute destructive changes in the spleen and thyroid gland, and the splenic tissue hardly regenerates at all in the irradiated mice (Betz, 1950; Palazzi and Pellegrini, 1952). Adrenalectomy somewhat lowered the involution of the spleen in rats, irradiated with X-rays in a dose of 200 r (Douglass and others, 1955). The lymphopenia, which arose after irradiation, was retarded by adrenalectomy either only in the first hours after irradiation (P. D. Gorizontov, A. A. Grafov, V. V. Shikhodyrov, 1958), or after the use of small (of the order of 10r) irradiation doses (Dougherty and White, 1946).

The participation of the corticosteroids in the regeneration of myelopoiesis after irradiation has been worked out in detail in the works of Betz, who has shown (1951, 1953), that the adrenalectomy of rats four days before irradiation with a dose of 500 r considerably retarded the regeneration of myelopoiesis and erythropoiesis. The administration of desoxycorticosterone acetate facilitated the formation of islets of myelopoiesis in the spleen of adrenalectomized and irradiated rats. An analogous influence on myelopoiesis in the spleen and the bone marrow was exerted by the administration of the somatotropic hormone of the hypophysis. The author assumes, however, that the action of the somatotropic hormone was mediated via its influence on the intensification of the processes of protein synthesis in general. In the presence of intact adrenals this action of the somatotropic hormone is absent, which can be explained as due to the action of cortisone on hematopoiesis in the irradiated animals, an action which is opposite to that of desoxycorticosterone-acetate and the somatotropic hormone. The administration of cortisone to rats, irradiated with X-rays in a

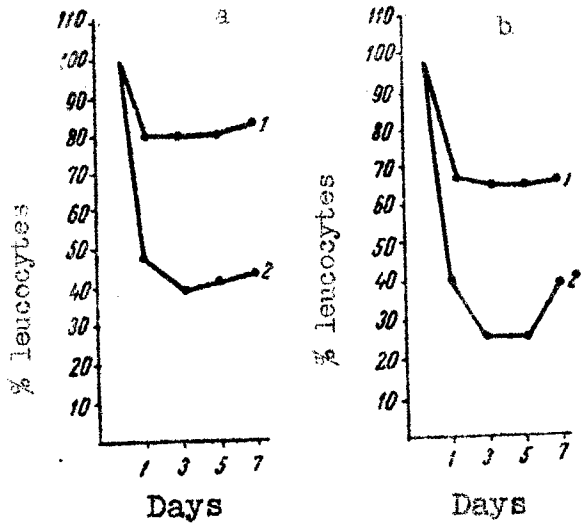

Fig. 2

a - change in the quantity of leucocytes (in percentages) after systemic irradiation of rats in a dose of 100 r: 1 - in intact; 2 - in hypophysectomized rats; b - change in the quantity of lymphocytes (in percentages) after systemic irradiation of rats in a dose of 100 r; 1 - in intact; 2 - in hypophysectomized rats.

dose of 500 r, in the period of one to eight days after irradiation considerably retarded the regeneration of myelopoiesis; however, if the regeneration has already begun, then the administration of cortisone (in the period of 8-11 days) did not change it. In contrast to this, the regeneration of the lymphopoiesis was sharply inhibited in the presence of the administration of cortisone independently of the period of its administration (Betz, 1952, 1955, 1957-1958).

In one of his works (1953) Betz showed that adrenalectomy four days before X-ray irradiation of rats in a dose of 500 r stimulated the regeneration of myelopoiesis; this was manifested in the appearance of hepatic foci of myelopoiesis. The data of this investigation contradict the earlier work (1951) of this same

author; it is possible that this is explained by the fact that in the early work only the bone marrow and the spleen were investigated. However, it is nonetheless evident, that the hypersecretion of the hormones of the adrenal cortex of the cortisone type which arises on the third to fourth day after irradiation negatively influences the regeneration of hematopoiesis and lowers the favorable action of hormones of the desoxycorticosterone type which, apparently, also occasions the negative influence of cortisone used with a therapeutic purpose (Tiersch and others, 1952; Wentworth and Billows, 1952; Friedman and others, 1954).

The participation of other endocrine glands in the regeneration of hematopoiesis after irradiation has still been insufficiently studied. The removal of the thyroid gland in irradiated rats (700 r) evoked a more profound and prolonged leucopenia and anemia and retarded the regeneration of hematopoiesis (Kretchmar and others, 1952); the administration of thiourea to rats, irradiated in a dose of 500 r, also retarded hematopoiesis (Betz, 1952). The administration of an extract of the thyroid gland exerted a certain stimulating influence on lymphopoiesis on guinea pigs irradiated with a dose of 300 r (Comsa, 1956).

The far from complete data presented attest to the important role of hormones of the adrenal cortex and of the hypophysis in the development of radiation injury. Consequently, many foreign authors are inclined to consider the radiation influence an ordinary "stressor," while the subsequent changes of the systems and functions are considered as the development of a general adaptational syndrome. This is indicated bh the increase in the lipids in the adrenal cortex in the rabbit after irradiation, (Nizet and others, 1959), by the increase in glycogen in the liver of rats, (Nims, Sutton, 1954; Mole, 1956), and by the relative resistance of mice and rats to repeated irradiation conducted in the mobilization phase, which was evoked by preliminary irradiation (E. H. Betz, 1950; A. A. Rogov, V. B. Rozen, 1959). The adaptation syndrome also arises in the presence of local irradiation (Langendorf, Lorenz, 1952). However, it is impossible to explain all the manifestations of radiation injury by the "stress" reaction alone. There is no doubt that irradiation evokes this reaction, but its course is different from the reactions arising in the presence of the action of other stimuli. The cause of this can be the simultaneous influence of irradiation on all systems, organs, and tissues of the animal in contrast to the action of other pathogenic stimuli. In this connection the development of the adaptational syndrome from the very beginning proceeds against a background of a changed state of the entire organ-

ism. Consequently, the adaptational syndrome can be of a different character, and the irradiation dose has great significance. In the presence of a gradual rise in the irradiation dose, the excretion of corticosteroids (and 17-ketosteroids) with the urine is distinctively changed (Rajewsky, 1956, Fig. 3): a rise in the irradiation dose to 800 r evokes an increase in the excretion of corticosteroids, and beginning with a dose of 1,000 r the phase of raised excretion disappears, and after irradiation there takes place only a reduction in the excretion of corticosteroids. This indicates a falling off of the "alarm reaction" phase or, as we have called it, the mobilization reaction. Analogous data were also obtained in the investigation of corticosteroids with the urine in patients, subjected to profound X-ray therapy on account of cancer (Maurer, 1954), and in the investigation of the reaction of the blood in the presence of various irradiation doses of adrenalectomized and hypophysectomized rats (P. D. Gorizontov and A. A. Grafov). Data concerning the change of the ordinary reaction of irradiated animals to insulin (D. A. Golubentsev, 1958) and adrenalin (B. M. Grayevskaya and R. Ya. Keylina, 1959) also indicate the possibility of a special course of the "stress" reaction.

The "stress" state and the adaptation syndrome, which appears to be a clinical manifestation of this state, cannot be considered as a reaction, occasioned only by the hormonal hypophysis - adrenal cortex system. In the formation of the response reaction of the organism, which, according to I. P. Pavlov, has received the designation of a "physiological measure against disease," diverse mechanisms undoubtedly participate including, in the first place, the nervous system. In this connection, one must speak of the interconnection of the endocrine and the nervous system in the irradiated organism. Without going into a discussion of the large number of works, devoted to the change in the nervous system in the presence of radiation disease, one can state that the higher regulation of the endocrine glands, both normally, and also after irradiation, probably is basically (if not wholly) effectuated via the hypothalamus and the hypophysis. The results of experiments involving the transplantation of the hypophysis of rats into the anterior chamber of the eye (Bacq and others, 1956) have shown that in these rats after irradiation the content of cholesterol in the adrenals is raised (in place of the usual lowering in intact rats). In contrast to this, the transplantation of the adrenals does not change their reaction to irradiation (Bacq, and others, 1956, 1957; Wyman and others, 1954, 1958).

As the experimental electrophysiological investigations of M. N. Livanov (M. N. Livanov and D. A. Biryukov, 1959)

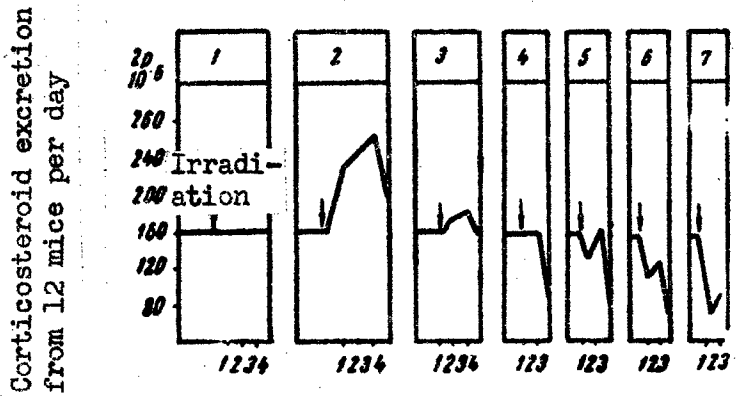

Fig. 3. Excretion of corticosteroids in mice after systemic irradiation with X-rays in the following doses:

1 - 100 r, 2- 350 r, 3- 800 4, 4 - 1,000 r, 5 - 1,200 r, 6 - 2,500 r, 7 - 20,000 r. The arrow designates the moment of irradiation.

and his co-workers have shown, in the presence of acute radiation sickness of rabbits there takes place a progressing worsening of the function of the subcortical centers.

It is now already well known that the higher nervous activity undergoes significant changes after irradiation. It can exert an influence on all functions and systems of the organism. However, the state of the higher nervous activity in irradiated animals in its turn to a certain extent depends on the function of the adrenals (A. A. Grafov, 1959). Thus, the materials present attest to the fact, that it is impossible to ascribe the reaction of the irradiated organism to change in the hormonal system (hypophysis-adrenals) alone.

Various forms of ionizing radiation evoke diverse direct and mediated reactions of various systems of the organism. Such a polypathogenetic action of irradiation represents one of the characteristic features of the injuring influence of radiation (P. D. Gorizontov). Consequently, we can not consider radiation

injury only as a syndrome of adaptation, evoked by a "stress" reaction. In the development of radiation disease an important role undoubtedly belongs to direct action, change of the humoral medium, the nervous system, and various glands of internal secretion, the role of which, however, has still been studied less than the hypophysis and adrenal cortex.

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